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(54) Title: NEMORUBICIN AS RADIOSENSITIZER IN COMBINATION WITH RADIATION THERAPY AGAINST TUMORS

(57) Abstract: The present invention relates to a morpholinyl anthracycline derivative for use as radiosensitizer, to be administered in combination with radiation therapy, so that a synergistic effect can be revealed.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X, P | WO 03/082267 A (TURSI JENNIFER MARGARET ; FOWST CAMILLA (IT); GERONI MARIA CRISTINA RO) 9 October 2003 (2003-10-09) page 1, paragraph 1 page 4, paragraph 3 – page 4, line 21 ----- | 1-15 |
| X | "The combination of nemorubicin with cisplatin and mitomycin C is synergistic in experimental tumor models" November 2002 (2002-11), EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, PAGE(S) S20 , XP004403486 ISSN: 0959-8049 abstract ----- -/- | 1-18 |

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| X | KABUTO M ET AL: "Antitumor effect of MX2, a new morpholino anthracycline against C6 glioma cells and its combination effect with photodynamic therapy in vitro!" October 1995 (1995-10), NO TO SHINKEI. BRAIN AND NERVE. OCT 1995, VOL. 47, NR. 10, PAGE(S) 969 - 973 , XP009033767 ISSN: 0006-8969 abstract | 1-3,6-15 |
| X | "Preclinical activity against liver metastases of Nemorubicin, a DNA-intercalating cytotoxic agent for the treatment of hepatocellular carcinoma" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, November 2002 (2002-11), page S19, XP004403483 ISSN: 0959-8049 abstract | 1-14 |
| X | "Properties of the new anthracycline derivative containing modified daunosamine moiety" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 38, November 2002 (2002-11), pages S19-S20, XP004403485 ISSN: 0959-8049 abstract | 1-15 |
| X | US 4 672 057 A (BARGIOTTI ALBERTO ET AL) 9 June 1987 (1987-06-09) cited in the application the whole document | 1-15 |
| X | US 4 710 564 A (MIZOBUCHI SHIGEYUKI ET AL) 1 December 1987 (1987-12-01) cited in the application the whole document | 1-15 |
| X | GB 2 315 067 A (PHARMACIA SPA ; PHARMACIA & UPJOHN SPA (IT)) 21 January 1998 (1998-01-21) cited in the application the whole document | 1-15 |
| X | GB 2 296 495 A (PHARMACIA SPA ; ERBA CARLO SPA (IT)) 3 July 1996 (1996-07-03) cited in the application the whole document | 1-15 |
| | | -/- |

INTERNATIONAL SEARCH REPORT

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PCT/EP2004/050246

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|--|
| Y | BONNER J A ET AL: "Doxorubicin decreases the repair of radiation-induced DNA damage" 1990, INTERNATIONAL JOURNAL OF RADIATION BIOLOGY 1990 UNITED KINGDOM, VOL. 57, NR. 1, PAGE(S) 55-64 , XP009033771 ISSN: 0020-7616 abstract ----- BONNER J A ET AL: "DOXORUBICIN ENHANCES RADIATION-INDUCED DNA DAMAGE" INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, vol. 15, no. SUPPL. 1, 1988, page 163, XP009033770 & 30TH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY, NEW ORLEANS, LOU ISSN: 0360-3016 abstract ----- WU LI-TEH: "Doxorubicin as radiation potentiator: Concurrent doxorubicin and radiation therapy interaction and its clinical applications" INFUSION CHEMOTHERAPY: IRRADIATION INTERACTIONS: PRINCIPLES AND APPLICATIONS TO ORGAN SALVAGE AND PREVENTION OF SECOND PRIMARY NEOPLASMS ELSEVIER SCIENCE PUBLISHERS B.V., PO BOX 211, SARA BURGERHARTSTRAAT 25, 1000 AE AMSTERDAM, THE NETHERLANDS; ELSEV, 1998, pages 147-151, XP002289046 ISSN: 0-444-82608-4 the whole document ----- JAGETIA GANESH CHANDRA ET AL: "Effect of doxorubicin on cell survival and micronuclei formation in HeLa cells exposed to different doses of gamma-radiation" STRAHLENTHERAPIE UND ONKOLOGIE, vol. 176, no. 9, September 2000 (2000-09), pages 422-428, XP002289047 ISSN: 0179-7158 abstract ----- CHENOUFI NORCHEN ET AL: "In vitro demonstration of synergy between radionuclide and chemotherapy" JOURNAL OF NUCLEAR MEDICINE, vol. 39, no. 5, May 1998 (1998-05), pages 900-903, XP009033769 ISSN: 0161-5505 abstract ----- | 1-15 1-15 1-15 1-15 1-15 1-15 1-15 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050246

| Patent document cited in search report | | Publication date | | Patent family member(s) | Publication date |
|--|---|------------------|----|-------------------------|------------------|
| WO 03082267 | A | 09-10-2003 | WO | 03082267 A1 | 09-10-2003 |
| US 4672057 | A | 09-06-1987 | GB | 2172594 A | 24-09-1986 |
| | | | BE | 904431 A1 | 16-07-1986 |
| | | | BG | 60535 B2 | 28-07-1995 |
| | | | BR | 1100255 A3 | 02-04-2002 |
| | | | CZ | 9104195 A3 | 17-03-1993 |
| | | | DE | 3609052 A1 | 25-09-1986 |
| | | | HK | 37392 A | 04-06-1992 |
| | | | JP | 1791944 C | 14-10-1993 |
| | | | JP | 4082160 B | 25-12-1992 |
| | | | JP | 61221194 A | 01-10-1986 |
| | | | MX | 9203114 A1 | 01-07-1992 |
| US 4710564 | A | 01-12-1987 | JP | 1049357 B | 24-10-1989 |
| | | | JP | 1564850 C | 25-06-1990 |
| | | | JP | 61167696 A | 29-07-1986 |
| | | | JP | 62016495 A | 24-01-1987 |
| | | | AT | 49412 T | 15-01-1990 |
| | | | CA | 1292225 C | 19-11-1991 |
| | | | DE | 3668173 D1 | 15-02-1990 |
| | | | EP | 0188293 A1 | 23-07-1986 |
| GB 2315067 | A | 21-01-1998 | DE | 69710573 D1 | 28-03-2002 |
| | | | DE | 69710573 T2 | 31-10-2002 |
| | | | WO | 9802446 A1 | 22-01-1998 |
| | | | EP | 0889898 A1 | 13-01-1999 |
| | | | JP | 11513040 T | 09-11-1999 |
| GB 2296495 | A | 03-07-1996 | DE | 19547958 A1 | 27-06-1996 |
| | | | IT | MI952614 A1 | 24-06-1996 |
| | | | JP | 8231581 A | 10-09-1996 |